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Synthesis of 1,3-Oxaselenan-2-imines from Isoselenocyanates

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The reactions of aryl isoselenocyanates **1** with 3-chloropropan-1-ol (**8**) in the presence of sodium hydride in dichloromethane at room temperature gave 1,3-oxaselenan-2-imines **10** in fair yield. A reaction mechanism *via* nucleophilic attack of the alcoholate at the isoselenocyanate **1**, followed by an *exo-6-tet* cyclization, is most likely.

Key words: isoselenocyanates, 1,3-oxaselenan-2-imines, selenaheterocycles, cyclizations

Selenium-containing heterocycles are of increasing interest because of their unique biological and pharmaceutical activities, *e.g.* as antitumor, antibacterial, and antiviral compounds, as enzyme inhibitors, and antioxidants [1]. Therefore, safe procedures for their synthesis, and easily accessible, stable and less toxic selenium reagents are much sought-after. In the last few years, we have shown that isoselenocyanates fulfil these conditions to a large extent, as they are easy to prepare [2] and are safe to handle and to store. Furthermore, they usually react under mild conditions, which are compatible with low stability of substrates and are tolerated by various functional groups. As a part of our research program aiming at developing new and simple procedures for the synthesis of selenium-containing heterocycles (see [3,4]), we have shown that aryl isoselenocyanates **1** are convenient precursors for the introduction of selenium into four [5] (see also [6]), five [7,8], six [7,9,10], and seven-membered selenaheterocycles [11]. The general concepts for the syntheses are shown in Scheme 1. The addition of a nucleophile **2**, which bears also a leaving group, leads to the

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intermediate **3**. Cyclization of the latter *via* the more nucleophilic Se-atom yields the selenaheterocycle of type **4**. The same concept has been used by Koketsu et al. for the synthesis of 5-methylene-1,3-selenazolidin-2-imines from **1** and propargylamine [12]. Alternatively, the adduct **5** of a bis-nucleophile, *e.g.* hydrazine, reacts with a bis-electrophile to give **6**, which undergoes a ring-closure to yield **7**.

Scheme 1

To the best of our knowledge, no report on the preparation of 1,3-oxaselenane exists, and only a few papers concern fused benzo-1,3-oxaselenanes [13]. Furthermore, there is not much known about O,Se-containing heterocycles in general, and most papers are devoted to molecular and analytical studies [14,15] and the synthesis of 1,4-oxaselenanes using potassium selenocyanate [16], selenium oxide [17], or hydrogen selenide [18].

In the present paper, we report the first synthesis of 2-imino-1,3-oxaselenanes by using aryl isoselenocyanates **1**.

RESULTS AND DISCUSSION

According to the general concept depicted in Scheme 1, we aimed at the preparation of 1-oxa-3-selenaheterocycles by the reaction of *ω*-haloalkan-1-ols with aryl isoselenocyanates **1**. Therefore, a mixture of **1** and 3-chloropropanol (**8**) in dichloromethane at room temperature was treated with an equimolar amount of sodium hydride, and the mixture was stirred for 3–4 h[**]. After chromatographic work up, an oily product, which contains aromatic as well as aliphatic H-atoms (^{1}H-NMR), was obtained in 36–60% yield. Mass spectrometry and elemental analysis confirmed that the two starting materials had reacted to yield the product by elimination of HCl. As we expected that the anion of **8** adds to **1** to give the intermediate **9** (Scheme 2), there are two possibilities for the cyclization reaction to be discussed: nucleophilic substitution of the chloride by the selenide would lead to 2-imino-1,3-oxaselenane **10** (path a)), whereas the analogous cyclization *via* the N-atom would yield 1,3-oxazinane-2-selones **11** (path b)). Both pathways are based on an *6-Exo-Tet* cyclization [19],

[**] It has to be noted that only this procedure led to a reaction between **1** and **8**. All attempts to prepare the alcoholate first led to reactions of the alcoholate with **8**.

and both have been observed previously in similar reactions, *i.e.* path a) [4–12] and path b) [20–22].

Scheme 2

On the basis of their spectroscopic data, the structure for the products was determined as **10**. For example, **10a** shows a strong IR absorption at 1662 cm^{-1} (C=N); the corresponding absorption of the N-analogue **12** appears at 1630 cm^{-1} [10] (see also [9]). The ^{1}H- and ^{13}C-NMR spectra of **10a** are very similar to those of the 1,3-selenazinan-2-imines **12** [10] (Figure 1). The only significant differencies concern C(2) and C(6), *i.e.*, the neighboring atoms of the O-atom, which are shifted to lower field. Furthermore, the H-atoms at C(6) absorb at 4.26 ppm in **10a** compared with 3.41 ppm in **12**. In the alternative structure **11** (Scheme 2), C(2) as well as C(4) should absorb at significantly lower field; the ^{13}C-absorptions for C(4), C(5), and C(6) of **11** would be expected at *ca*. 45, 24, ad 70 ppm, respectively.

Figure 1. Chemical shifts (ppm) of H- and C-atoms of **10a** and **12** in $CDCl_3$.

All attempts to generalize the reaction toward the synthesis of 5- and 7-membered analogues of **10** failed. Neither in the case of 2-haloethanol nor in the case of 4-halobutan-1-ol could addition products be obtained.

In conclusion, we have shown that the base-catalyzed reaction of 3-chloropropan-1-ol (**8**) with aryl isoselenocyanates **1** yields derivatives of the almost unknown 1,3-oxaselenanes. The synthesis uses **1** as an easily accessible and safe selenium-containing starting material, which is smooth to handle.

EXPERIMENTAL

1. General. Thin layer chromatography (TLC): silica gel 60 F_{254} plates (0.25 mm; Merck). Column chromatography (CC): silica gel 60 (0.040–0.063 mm; Merck). Melting points (M.p.) were determined in capillaries on a Büchi B-540 apparatus and are not corrected. The IR spectra were registered on a Perkin-Elmer 1600-FT-IR spectrometer (as film). The NMR spectra were recorded in $CDCl_3$ solutions on a Bruker ARX-300 instrument

(^{1}H: 300 MHz; ^{13}C: 75.6 MHz); chemical shifts in ppm relative to internal TMS. The ^{13}C-NMR spectra were recorded by using DEPT registration. The CI-MS spectra were registered with a Finnigan SSQ-700 or MAT-90 instrument; NH_3 as carrier gas.

2. Starting materials. 3-Chloropropan-1-ol (**8**) and sodium hydride (95%) are commercially available (Fluka and Aldrich). Isoselenocyanates **1a**–**d** were prepared according to Bartons procedure [2] starting from formamides. Formanilide is commercially available (Fluka and Aldrich), *N*-(4-chlorophenyl)-, *N*-(4-bromophenyl)-, and *N*-(4-methylphenyl)formamide were prepared from the respective commercial aniline and 95% formic acid [23]. The solution was heated to reflux for 30 min and evaporated to dryness in vacuo. The residue was dissolved in ether and washed with diluted acetic acid (5%), water, and aqueous $NaHCO_3$ (5%). The aqueous layer was extracted with ether, the combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The crude products were purified by recrystallization in ethanol/water.

3. General procedure for the synthesis of 1,3-oxaselenan-2-imines. A 25 mL round-bottom flask equipped with magnetic stirrer and condenser was charged with a mixture of an isoselenocyanate **1** (1.0 mmol) and 3-chloropropan-1-ol (**8**, 1.0 mmol) in dichloromethane (20 ml). Then, sodium hydride (ca. 1.0 mmol) was added, the reaction mixture was stirred for 3 to 4 h at room temperature and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (100/0 to 50/50) as eluant.

(1,3-Oxaselenan-2-ylidene)(phenyl)amine (**10a**). Yield: 86.5 mg (36%), yellow oil. IR (film): 3442*m* (br), 3060*w*, 2926*w*, 1726*w*, 1662*s*, 1628*s*, 1592*s*, 1539*w*, 1493*m*, 1441*w*, 1371*w*, 1288*w*, 1231*m*, 1150*w*, 1067*w*, 1023*w*, 1002*w*, 866*w*, 765*m*, 696*s*. ^{1}H-NMR ($CDCl_3$): 2.03–2.13 (*m*, CH_2); 2.93 (*t*, *J* = 7.2, CH_2); 4.26 (*t*, *J* = 7.2, CH_2); 6.82 (*d*, *J* = 8.1, 2 arom. H); 7.01 (*t*, *J* = 8.1, 2 arom. H); 7.22 (*d*, *J* = 8.1, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 20.2 (CH_2); 23.2 (CH_2); 70.1 (CH_2); 121.3 (2 arom. CH); 124.1 (1 arom. CH); 129.0 (2 arom. CH); 146.8 (arom. C); 152.7 (C=N). CI-MS: 244 (18), 243 (12), 242 (100, [M(^{80}Se)+1]$^+$), 241 (14), 240 (53), 239 (23), 238 (22). Anal. Calc. for $C_{10}H_{11}NOSe$ (240.17): C 50.01, H 4.62, N 5.83. Found: C 49.88, H 4.45, N 6.01.

(4-Bromophenyl)(1,3-oxaselenan-2-ylidene)amine (**10b**). Yield: 127.6 mg (40%), orange oil. IR (film): 3442*w* (br), 3234*w*, 3102*w*, 3030*w*, 2960*w*, 1694*w*, 1652*s*, 1597*w*, 1586*w*, 1552*m*, 1486*s*, 1440*w*, 1423*w*, 1393*m*, 1302*m*, 1285*m*, 1260*w*, 1245*m*, 1159*m*, 1111*w*, 1099*w*, 1069*m*, 1009*m*, 881*w*, 814*m*, 798*m*, 714*w*, 652*w*, 615*w*. ^{1}H-NMR ($CDCl_3$):

2.10–2.21 (*m*, CH_2); 3.01 (*t*, *J* = 7.2, CH_2); 4.33 (*t*, *J* = 7.2, CH_2); 6.74, 7.37 (*AA'BB'*, *J* = 8.1, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 20.4 (CH_2); 23.2 (CH_2); 70.2 (CH_2); 117.1 (1 arom. C); 123.2 (2 arom. CH); 132.1 (2 arom. CH); 145.8 (1 arom. C); 153.2 (C=N). CI-MS: 324 (12), 323 (10), 322 (76), 321 (19), 320 (100, $[M(^{80}Se,^{79}Br)+1]^+$), 319 (26), 318 (47), 317 (17), 316 (16). Anal. Calc. for $C_{10}H_{10}BrNOSe$ (319.01): C 37.64, H 3.16, N 4.39. Found: C 37.77, H 3.22, N 4.12.

(4-Chlorophenyl)(1,3-oxaselenan-2-ylidene)amine (**10c**). Yield: 129.78 mg (47%), orange oil. IR (film): 3425*w* (br), 2928*w*, 2857*w*, 1726*w*, 1662*s*, 1628*s*, 1589*m*, 1532*w*, 1489*s*, 1435*w*, 1401*w*, 1371*w*, 1235*m* (br), 1172*w*, 1151*w*, 1091*m*, 1066*w*, 1012*m*, 877*w*, 831*m*, 720*w*. ^{1}H-NMR ($CDCl_3$): 2.17–2.33 (*m*, CH_2); 3.08 (*t*, *J* = 7.2, CH_2); 4.39 (*t*, *J* = 7.2, CH_2); 6.85, 7.29 (*AA'BB'*, *J* = 8.1, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 20.3 (CH_2); 23.2 (CH_2); 70.2 (CH_2); 122.7 (2 arom. CH); 129.1 (2 arom. CH); 130.8 (1 arom. C); 145.3 (1 arom. C); 154.2 (C=N). CI-MS: 278 (44), 277 (12), 276 (100, $[M(^{80}Se)+1]^+$), 275 (12), 274 (49), 273 (16), 272 (17). Anal. Calc. for $C_{10}H_{10}NOSeCl$: C 43.74, H 3.67, N 5.10. Found: C 43.88, H 3.54, N 5.20.

(4-Methylphenyl)(1,3-oxaselenan-2-ylidene)amine (**10d**). Yield: 152.5 mg (60%), orange oil. IR (film): 3424*w* (br), 3301*w*, 3038*w*, 2924*m*, 2866*w*, 1722*w*, 1696*m*, 1664*s*, 1602*w*, 1511*s*, 1441*w*, 1406*w*, 1372*w*, 1313*w*, 1288*w*, 1235*m* (br), 1178*w*, 1107*w*, 1066*w*, 877*w*, 819*s*, 720*m*. ^{1}H-NMR ($CDCl_3$): 2.19–2.30 (*m*, CH_2); 2.32 (*s*, CH_3); 3.02 (*t*, *J* = 7.2, CH_2); 4.36 (*t*, *J* = 7.2, CH_2); 6.87, 7.10 (*AA'BB'*, *J* = 8.1, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 20.1 (CH_2); 20.8 (CH_3); 23.3 (CH_2); 70.0 (CH_2); 119.2 (1 arom. C); 121.1 (2 arom. CH): 129.6 (2 arom. CH); 133.0 (1 arom. C); 144.1 (1 arom. C); 153.0 (C=N). CI-MS: 258 (18), 257 (15), 256 (100, $[M(^{80}Se)+1]^+$), 255 (24), 254 (51), 253 (27), 252 (23), 251 (4). Anal. Calc. for $C_{11}H_{13}NOSe$ (254.20): C 51.98, H 5.15, N 5.51. Found: C 52.28, H 5.02, N 5.87.

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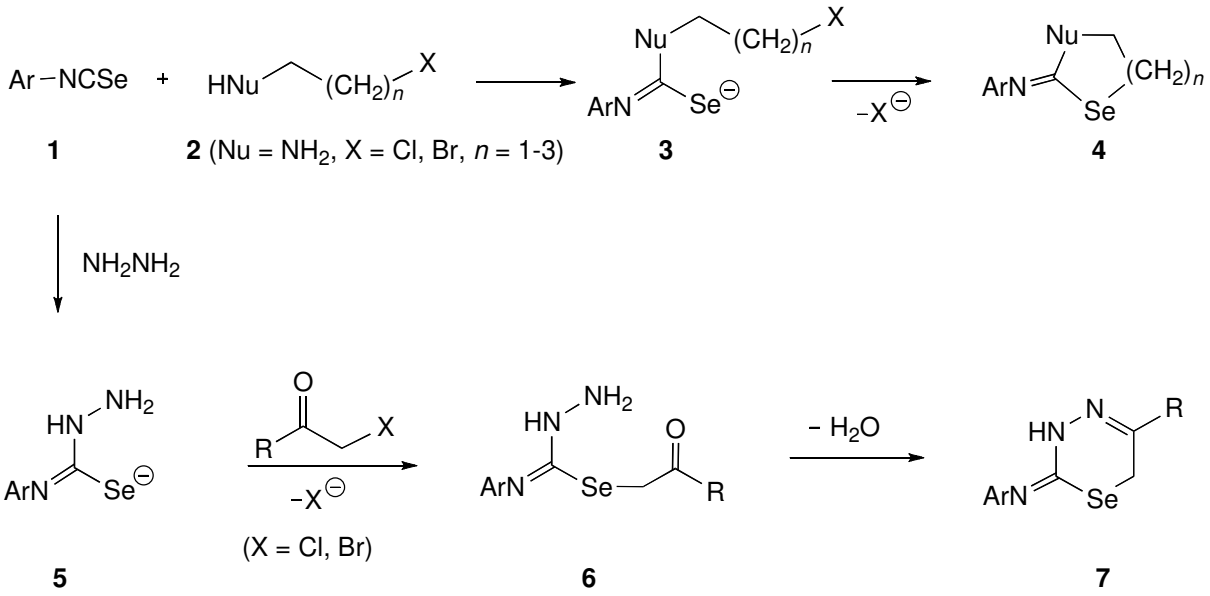
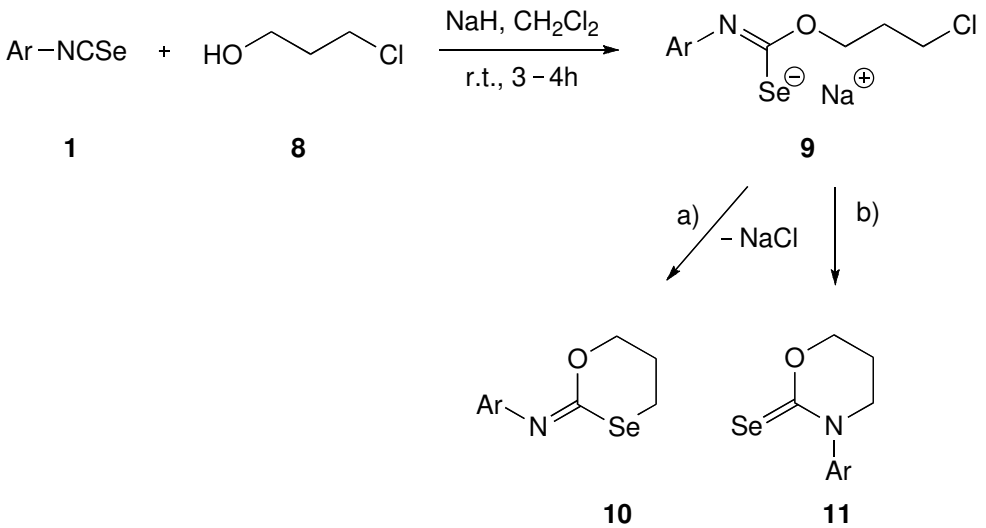
Scheme 1



1 **2** (Nu = NH_2, X = Cl, Br, *n* = 1-3) **3** **4**

5 **6** **7**

Scheme 2

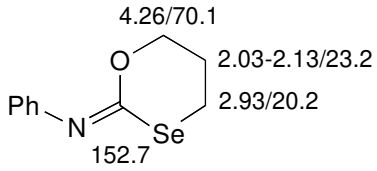


1 **8** **9**

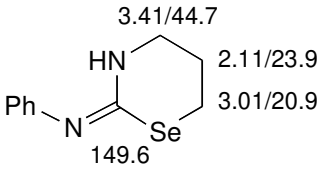
10 **11**

a: Ar = Ph, **b**: Ar = 4-BrC_6H_4 **c**: Ar = 4-ClC_6H_4 **d**: Ar = 4-MeC_6H_4

Figure 1



10a



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